UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/352,466	07/13/1999	VIRGINIA C BROUDY	A-195CDD	2305

21069 7590 02/28/2005

AMGEN INC.
MAIL STOP 27-4-A
ONE AMGEN CENTER DRIVE
THOUSAND OAKS, CA 91320-1799

EXAMINER	
HELMS, LARRY RONALD	
ART UNIT	**PAPER NUMBER**
1642	

DATE MAILED: 02/28/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

HL

Office Action Summary	Application No.	Applicant(s)	
	09/352,466	BROUDY ET AL.	
	Examiner	Art Unit	
	Larry R. Helms	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *17 September 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *26-44* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *26-44* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 9/17/04 has been entered.

2. Claims 1-25 have been cancelled.

Claim 26 has been amended.

3. The text of those sections of Title 35 U.S.C. code not included in this office action can be found in a prior Office Action.

4. The following Office Action contains NEW GROUNDS of rejections.

5. Claims 26-44 are pending and under examination.

Rejections Withdrawn

6. The rejection of claims 26-44 under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention is withdrawn in view of the amendments to the claims.

7. The rejection of claims 26-44 under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most

nearly connected, to make and/or use the invention is withdrawn in view of the amendments to the claims.

8. The rejection of claims 27-28 under 35 U.S.C. § 112, first paragraph, because the specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention, because the specification does not provide evidence that the claimed biological materials are (1) known and readily available to the public; (2) reproducible from the written description is withdrawn in view of the declaration of Virginia Broudy and that all assurances have been met.

The following are NEW GROUNDS of Rejections

Claim Rejections - 35 USC § 112

9. Claims 26-44 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

A. Claims 26-44 are indefinite for reciting a method of treating cancer but claim 26 does not have all of the method steps to perform the method. The claim does not need the receptor containing cells to be cancerous. Are the cells

cancerous or not? In addition, claim 36 recites several cells of which two are cancerous, but and are the bone marrow and progenitor cells also cancerous?

B. Claim 32 is indefinite for reciting "essentially entirely" because does the phrase mean complete inhibition or only partially?

C. Claim 44 recites the trademark "Tween" and it is unclear what substances are encompassed by the term.

10. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

11. Claims 26-44 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a NEW MATTER rejection.

The claims are broadly drawn to a method of treating any cancer comprising administering to a patient a chemotherapeutic agent and an antibody. The response filed 9/17/04 stated that support for the claims was in the specification at page 20, line 19 to page 21, lines 21, page 17, line 25 to page 18, line 14 and original claims 14-16. The response has been carefully considered but found not to be persuasive. The claim encompasses a separate

chemotherapeutic agent and an antibody. At the recited pages the specification discloses antibodies useful for modifying the sensitivity to chemotherapeutic agents by administration of an antibody and to inhibit progenitor cells, leukemia, solid tumor and bone marrow cells (page 20-21) and the antibodies are used to treat neoplastic cells by administration of an anti-neoplastic therapeutic agent conjugated to the antibody and the neoplastic therapeutic agents are 125I, toxins (see page 17-18) and conjugates in original claims 14-16.

There appears to be some support for antibody conjugates with therapeutic agents but not chemotherapeutic agents. In addition there appears to be no support for a separate chemotherapeutic agent (what ever this compound is) and the antibody. The specification seems to have support for treating leukemia and solid tumors with an antibody therapeutic conjugate. Therefore, applicant is required to provide specific support for the claimed limitations in the specification as originally filed or remove them from the claims.

12. Claims 26-44 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is written description rejection.

The claims are drawn to an antibody which binds to an epitope on "A" receptor recognized by human stem cell factor. The specification only discloses

the proto-oncogene c-kit as the receptor for human stem cell factor (see page 1, lines 18-20). The specification does not have written description for any other receptors of any origin that stem cell factor binds to. Consequently, the specification does not provide an adequate written description of "a receptor recognized by human stem cell factor".

Adequate written description requires more than a mere statement that it is part of the invention. The sequence itself is required. See Fiers v. Revel, 25 USPQ2d 1601, 1606 (CAFC 1993) and Amgen Inc. V. Chugai Pharmaceutical Co. Ltd., 18 USPQ2d 1016.

Therefore, only the proto-oncogene c-kit meets the written description provision of 35 U.S.C. 112, first paragraph. Vas-Cath Inc. v. Mahurkar, 19 USPQ2d 1111, makes clear that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the written description inquiry, whatever is now claimed. (See page 1117.) The specification does not clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed. (See Vas-Cath at page 1116.). Consequently, Applicant was not in possession of the instant claimed invention. See University of California v. Eli Lilly and Co. 43 USPQ2d 1398.

Applicant is directed to the Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, ¶ 1 "Written Description" Requirement, Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001.

13. Claim 27 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is written description rejection.

The claim is drawn to an antibody that bind to an epitope recognized by the antibody produced by ATCC HB 10716. The specification does not disclose what linear residues or region or what combinations of residues would make up the amino acids in the epitope for the antibody to bind to. The specification does not have written description for any epitope that is recognized by the antibody produced by HB 10716. Consequently, the specification does not provide an adequate written description of "an epitope" recognized by the antibody.

Adequate written description requires more than a mere statement that it is part of the invention. The sequence itself is required. See Fiers v. Revel, 25 USPQ2d 1601, 1606 (CAFC 1993) and Amgen Inc. V. Chugai Pharmaceutical Co. Ltd., 18 USPQ2d 1016.

Therefore, only the proto-oncogene c-kit meets the written description provision of 35 U.S.C. 112, first paragraph. Vas-Cath Inc. v. Mahurkar, 19 USPQ2d 1111, makes clear that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the written description inquiry, whatever is now claimed. (See page 1117.) The

specification does not clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed. (See Vas-Cath at page 1116.). Consequently, Applicant was not in possession of the instant claimed invention. See University of California v. Eli Lilly and Co. 43 USPQ2d 1398.

Applicant is directed to the Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, ¶ 1 "Written Description" Requirement, Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001.

14. Claims 26-44 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of treating leukemia cells comprising administering to a patient a therapeutic conjugate of an antibody that binds to leukemia cells that have the c-kit receptor and wherein the antibody binds to an epitope on c-kit and inhibits binding to c-kit entirely and the conjugate decreases the growth rate of the leukemia cells and the antibody is humanized and pharmaceutical compositions comprising such, does not reasonably provide enablement for a method of treating just any cancer or any cell that just has any receptor recognized by stem cell factor. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Factors to be considered in determining whether undue experimentation is required, are summarized in Ex parte Forman, 230 USPQ 546 (BPAI 1986). They include the nature of the invention, the state of the prior art, the relative skill

of those in the art, the amount of direction or guidance disclosed in the specification, the presence or absence of working examples, the predictability or unpredictability of the art, the breadth of the claims, and the quantity of experimentation which would be required in order to practice the invention as claimed.

The claims are broadly drawn to treating just any cancer or wherein the patient does not have cancerous cells, only receptor containing cells or progenitor cells or bone marrow cells (not claimed to be cancerous, see claim 36). The specification discloses treating leukemia cells with toxins conjugated to an antibody binding to human stem cell factor (see page 4, lines 10-18). The specification discloses that stem cell factor is on solid tumors, and on some cancer cell lines (see page 26 and Figure 4). The specification does not enable other cancers other than leukemia as indicated below or by treating just any cell with a receptor recognized by stem cell factor.

One cannot extrapolate the teaching of the specification to the claimed invention because there is no guidance on or exemplification of any correlation between just treating just any cancer with an antibody to stem cell factor. The specification does not teach that such an antibody can treat cancer cells to decrease the growth of such cells by itself without conjugation to a therapeutic agent.

Further, one cannot extrapolate the teaching of the specification to the claims because Curti (Crit. Rev. in Oncology/Hematology, 1993, 14:29-39) teaches that solid tumors resist destruction by chemotherapy agents and that

although strategies to overcome defense mechanisms of neoplastic cells have been developed and tested in a number of patients, success has been limited and further teaches that it is certainly possible that cancer cells possess many as yet undefined additional molecular mechanisms to defeat chemotherapy treatment strategies and if this is true, designing effective chemotherapeutic regimens for solid tumors may prove a daunting task (para bridging pages 29-30) and concludes that knowledge about the physical barriers to drug delivery in tumors is a work in progress (p. 36, col 2). In addition, Jain (Sci. Am 271:58, 1994) discloses the art known barriers to the delivery of drugs into solid tumors. Impediments to drug delivery include (1) Nonuniform blood delivery to all areas of the tumor in which some areas of the tumor receive therapeutic agents and other areas of the tumor receive no therapeutic agent at all. (Page 60 col. 3); (2) Increased viscosity of blood in the tumor itself which also hinders drug delivery to the tumor (see paragraph bridging pages 60 and 61); (3) High liquid pressures in the interstitial matrix can retard the delivery of large therapeutic agents, such as antibodies, into tumors (page 61, Col. 1 paragraph 1); (4) Convection is a necessary mechanism by which larger therapeutics molecules such as antibodies, reach target cells which are not directly fed by the vasculature. Convection is not observed in large tumors (defined as more than ½ centimeter in diameter, page 62 col. 1) and convection is necessary for adequate drug delivery of molecules having a molecular weight of more than 5000 (page 61, col. 1 through page 63, col. 3) and (4) Molecules as large as antibodies (i.e.,

MW=150,000) would require several months to reach a uniform concentration in a tumor that measures 1 centimeter in radius (page 63, col. 2).

The specification provides insufficient guidance with regard to the issues raised above and provides no working examples which would provide guidance to one skilled in the art and no evidence has been provided which would allow one of skill in the art to predict the efficacy of the claimed methods with a reasonable expectation of success. In view of the above, one of skill in the art would be forced into undue experimentation to practice the claimed invention.

Claim Rejections - 35 USC § 103

15. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a

later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

16. Claims 26, 29-44 are rejected under 35 U.S.C. 103(a) as being unpatentable over Gadd et al (Leukemia Research 9:11:1329-36, 1985, IDS 10/99) as evidenced by Broudy et al (Blood 79:338-346, 1992), and further in view of Cambareri et al (Leukemia Research 12:929-939, 1988, Ids 10/99) and Hara et al (PNAS 84:3390-94, 1987) and Riechmann et al (Nature 332:323-27, 1988, IDS 10/99), and Byars et al Vaccine 5:223-8, 1987).

The claims recite a method of treating leukemia cells comprising administering to a patient a chemotherapeutic and an antibody that binds to leukemia cells that have the receptor and wherein the antibody binds to an epitope on the receptor and inhibits binding to the receptor entirely and the conjugate decreases the growth rate of the leukemia cells and the antibody is humanized and pharmaceutical compositions comprising such with phosphate buffer, sterile isotonic solution and Tween.

Gadd et al teach the antibody YB5.B8 which as evidenced by Broudy et al recognizes human c-kit and inhibits binding of stem cell factor (see page 342, right column). Gadd et al also teach the antibody binds to human leukemia cells and treating the cells with the antibody. Gadd et al does not teach a treatment method with a chemotherapeutic agent or humanized antibodies or pharmaceutical compositions of phosphate buffer, sterile, or Tween. These

deficiencies are made up for in the teachings of Cambareri et al, Hara et al, Riechmann et al, and Byars et al.

Cambareri et al teach the YB5.B8 antibody in sterile PBS (see page 930).

Hara et al teach complete suppression of human leukemia cells by immunotoxins using an antibody to an antigen on leukemia cells and ricin.

Riechmann et al teach methods of humanizing antibodies for therapy in humans.

Byars et al teach adding Tween 80 to proteins for formulations in human vaccines.

It would have been prima facie obvious to one of ordinary skill in the art at the time the claimed invention was made to have treated leukemia patients with a conjugate of an antibody that inhibits the binding of stem cell factor to its receptor and decreases the growth rate of the cells and the antibody was humanized and the antibody was in a pharmaceutical composition.

One of ordinary skill in the art would have been motivated to and had a reasonable expectation of success to have treated leukemia patients with a conjugate of an antibody that inhibits the binding of stem cell factor to its receptor and decreases the growth rate of the cells and the antibody was humanized and the antibody was in a pharmaceutical composition because Gadd et al teach adding the antibody to leukemia cells to treat the cells and the antibody inhibits the binding to the receptor. It would have been obvious to put the antibody in a pharmaceutical composition because Cambareri et al does such in PBS and is sterile and performs experiments with such formulations. In addition, one of

ordinary skill in the art would have been motivated to and had a reasonable expectation of success to have treated leukemia patients with a conjugate of an antibody that inhibits the binding of stem cell factor to its receptor and decreases the growth rate of the cells and the antibody was humanized and the antibody was in a pharmaceutical composition because Hara et al teach the treatment of leukemia patients with an immunotoxin where the antibody targets the cells and the toxin destroys the cells. It would have been obvious to treat leukemia with a toxin conjugate because Hara teach such and it would have been obvious to treat cells with the c-kit receptor because such an antibody was used for detecting cells (see Gadd et al) and it is obvious that one would want to kill such eulogia cells with a toxin. Because the immunoconjugate of Hara et al completely suppressed the tumor growth it would be obvious that the limitation of decreasing the growth rate of the cells is met when using such a conjugate toxin (for claims 33-35). In addition, one of ordinary skill in the art would have been motivated to and had a reasonable expectation of success to have treated leukemia patients with a conjugate of an antibody that inhibits the binding of stem cell factor to its receptor and decreases the growth rate of the cells and the antibody was humanized and the antibody was in a pharmaceutical composition because Riechmann et al teach humanization of antibodies from the hybridoma and this is routine for producing antibodies for treatment in humans to avoid anti-immunoglobulin responses using a murine antibody. In addition, one of ordinary skill in the art would have been motivated to and had a reasonable expectation of success to have treated leukemia patients with a conjugate of an antibody that

inhibits the binding of stem cell factor to its receptor and decreases the growth rate of the cells and the antibody was humanized and the antibody was in a pharmaceutical composition because Byars et al teach formulations of proteins with Tween 80 for human vaccines and it would have been obvious to formulate the antibody for treatment because such is routinely done.

Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references.

Conclusion

17. No claim is allowed.

18. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Larry R. Helms, Ph.D, whose telephone number is (571) 272-0832. The examiner can normally be reached on Monday through Friday from 6:30 am to 4:00 pm, with alternate Fridays off. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeffrey Siew, can be reached on (571) 272-0787.

19. Papers related to this application may be submitted to Group 1600 by facsimile transmission. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The Fax Center telephone number is (571) 273-8300.

Respectfully,

Larry R. Helms Ph.D.

571-272-0832

LARRY R. HELMS, PH.D
PRIMARY EXAMINER